Gynecologic Oncology Reports 55 (2024) 101467

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Use of indocyanine green dye for sentinel lymph node mapping in patients with endometrial cancer and a history of iodinated contrast allergy

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ARTICLE INFO

Keywords:
Sentinel lymph node mapping
Contrast allergy
Endometrial cancer
Indocyanine green dye

ABSTRACT

Objectives: Sentinel lymph node (SLN) mapping is a surgical technique with high accuracy in detecting metastases while limiting morbidity associated with full lymphadenectomy in endometrial cancer. Cervical injection of indocyanine green (ICG) dye is associated with very high SLN detection rates; however, iodinated contrast allergy has traditionally been viewed as a contraindication to ICG use. The objective of this study was to describe the use of ICG in a population of patients with iodinated contrast allergies undergoing surgical staging for endometrial cancer.

Methods: IRB approval was obtained. All patients with clinically early-stage endometrial cancer who underwent minimally invasive surgical staging with SLN mapping with ICG at a single academic institution from 1/1/2017 to 12/31/2020 were identified retrospectively. Patients with reported iodinated contrast allergies prior to surgery were identified. Data were collected through electronic medical record review and compared using descriptive statistics.

Results: 820 patients who underwent minimally invasive surgical staging with SLN mapping with ICG were identified, and 25 had documented iodinated contrast allergies. Documented reactions included rash/hives (n = 10, 40 %), anaphylaxis (n = 6, 24 %), shortness of breath (n = 5, 20 %), diarrhea (n = 1, 4 %), and not specified (n = 3, 12 %). A majority (24/25, 96 %) received 4 mg intravenous dexamethasone during induction of general anesthesia as per the institutional enhanced recovery after surgery (ERAS) protocol. No patients experienced allergic reactions or other adverse events after ICG injection.

Conclusions: No patients in this cohort demonstrated an adverse reaction after ICG injection for SLN mapping. This study supports the reasonable safety of ICG in patients with contrast allergies, particularly when routine ERAS protocols containing dexamethasone are utilized.

1. Introduction

Endometrial cancer remains the most common gynecological malignancy in the United States with an estimated 66,200 new diagnoses to occur in 2023 (American Cancer Society, 2023). Traditionally, the management of clinically early-stage endometrial cancer consisted of surgical staging with total abdominal hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic and *para*-aortic lymphadenectomy. Over the last two decades, evidence demonstrates that minimally invasive surgical techniques as well as selective lymphadenectomy based on uterine tumor factors are effective surgical staging strategies that do not compromise patient outcomes (Walker et al., 2009; Galaal et al., 2018; Mariani et al., 2008). More recently, sentinel lymph node (SLN) mapping has been shown to increase the detection of lymph node metastases with low false-negative rates and is the National Comprehensive Cancer Network (NCCN) preferred technique for lymph node sampling in appropriately selected patients (Holloway, 2017; Rossi, 2017).

SLN mapping involves intracervical injection with dye in both superficial and deep locations in order to deliver the dye to the main uterine lymphatic trunks. Various injection dyes have been utilized, including radiolabeled colloid (most commonly technetium-99), colored dyes, and indocyanine green (ICG). ICG is commonly used in SLN mapping for endometrial cancer given its relative ease of use as well as its high SLN detection rate (Rossi, 2017; Holloway et al., 2016).

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https://doi.org/10.1016/j.gore.2024.101467
Received 5 June 2024; Received in revised form 17 July 2024; Accepted 20 July 2024
Available online 21 July 2024

ICG is a lyophilized green powder containing indocyanine green and up to 5 % sodium iodide (IC-GREEN, 2006). Iodinated contrast allergies have traditionally been considered a contraindication to the use of ICG because of its sodium iodide component. As such, patients with a reported allergy to iodine or iodinated contrast were excluded in several of the major SLN mapping trials in endometrial cancer (Rossi, 2017; Frumovitz et al., 2018). Despite this theoretical risk, there are limited data on the true risk of cross-reactivity between iodinated contrast and ICG. Additionally, there are limited data on how this potential risk can be mitigated in patients with reported contrast allergies. The objective of this study was to describe the use of ICG in a population of patients with iodinated contrast allergies undergoing surgical staging for endometrial cancer.

2. Methods

This study was conducted under a research registry approved by the University of Pittsburgh Human Research Protection Office Institutional Review Board (STUDY20070350). All patients with clinically early-stage endometrial cancer who underwent minimally invasive surgical staging with SLN mapping at a single academic institution from 1/1/2017 to 12/31/2020 were identified retrospectively. Patients with a documented history of iodinated contrast allergies prior to surgery were identified. The medical record was reviewed for documented allergic reactions after ICG dye administration in the intraoperative setting and during postoperative recovery prior to discharge. The ERAS protocol for minimally invasive gynecologic surgery at our institution utilizes 4–5 mg intravenous dexamethasone during induction of general anesthesia (University of Pittsburgh Medical Center, 2023). Therefore, perioperative administration of corticosteroids or anti-allergic medications were assessed as well. Data were compared using descriptive statistics.

3. Results

A total of 820 patients underwent minimally invasive surgical staging with SLN mapping with ICG dye during this period. Within this cohort, 25 patients with a documented history of iodinated contrast allergy were identified (Table 1, Fig. 1). The mean age was 64.5 years (range 38–84), the mean body mass index was 35.8 kg/m^2 (range 18–53), and most patients (23/25, 92 %) were white. Reported allergic reactions to iodinated contrast included rash/hives (n = 10, 40 %), anaphylaxis (n = 6, 24 %), shortness of breath (n = 5, 20 %), diarrhea (n = 1, 4 %), and not specified (n = 3, 12 %). A majority of patients (24/25, 96 %) received 4 mg intravenous dexamethasone during induction of general anesthesia as per our institution's enhanced recovery after surgery (ERAS) protocol. No additional medications that could be considered prophylaxis against allergic reactions were administered to any patient. No patients experienced an allergic reaction or any other adverse event after intracervical injection of ICG.

Table 1
Clinical characteristics.

Clinical Variable	n (%) Total n = 25
Age, mean (range)	64.5 (38–84)
BMI, mean (range)	35.8 (18–53)
Race	
White	23 (92)
Black	1 (4)
Other	1 (4)
Documented Prior Contrast Allergy	
Rash/hives	10 (40)
Anaphylaxis	6 (24)
Shortness of Breath	5 (20)
Diarrhea	1 (4)
Not Specified	3 (12)
Received Preoperative Dexamethasone	
Yes	24 (96)
No	1 (4)

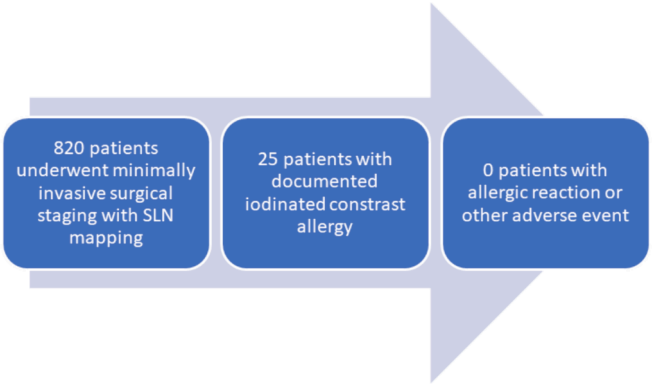

Fig. 1. Study flow diagram.

4. Discussion

In this cohort of patients with a history of iodinated contrast allergies, there were no patients who experienced an allergic reaction or any other adverse event after intracervical injection of ICG. This study provides evidence that supports the reasonable safety of ICG use for SLN mapping in patients with iodinated contrast allergies.

The use of intracervical ICG for SLN mapping in endometrial cancer patients has an excellent safety profile with a low incidence of allergic reactions or adverse events, as supported by three major prospective studies. The FIRES trial reported no allergic reactions associated with ICG use in their cohort of 385 patients, though patients with a history of iodinated contrast allergy were excluded from this trial (Rossi, 2017). Another prospective study included 204 patients without known or suspected iodine or contrast allergies and reported one delayed allergic reaction on postoperative day 6 which was possibly attributable to ICG (Backes, 2019). Paley et al reported no allergic reactions in their cohort of 123 patients who underwent SLN mapping with ICG injection, however, they did not report the patients' iodine or contrast allergy status (Paley, 2016).

There are limited data regarding the use of intracervical ICG injection in patients with endometrial cancer who have documented iodine or contrast allergies. A recent single institution report of 1414 consecutive patients undergoing SLN mapping with ICG, including 67 patients with a documented iodine or contrast allergy, reported no ICG-related allergic reactions or adverse events (Zammarrelli et al., 2021). Importantly, 97 % of patients in their cohort with iodine or contrast allergies received preoperative corticosteroids with or without diphenhydramine, often administered as part of their institution's standard antiemetic regimen.

In review of the literature, there is one reported case of anaphylactic reaction after intracervical injection of 40 mg of ICG (8 cc of a 5 mg/cc ICG solution), which is significantly higher than the doses routinely used in the United States (Papadia et al., 2017). The authors do not report if this patient had a history of iodine or contrast allergy, nor if the patient received any form of allergy premedication; however, the patient subsequently demonstrated a "slight reaction" to ICG in a prick test. There were no other reported allergic reactions or adverse events attributable to ICG in their single institution cohort of 258 patients, which included 176 patients who underwent ICG injection as part of endometrial cancer staging.

Taken in the context of the above literature, our study provides additional evidence that intracervical ICG injection is reasonably safe in patients with a history of iodine or contrast allergies, particularly when corticosteroid premedication is utilized. ERAS protocols have become an increasingly common practice and often include the administration of

multimodal analgesic and antiemetic medications in the perioperative setting (Altman et al., 2019). Nearly all patients with a contrast allergy in our cohort received preoperative dexamethasone as part of the standard ERAS protocol utilized at our institution. Dexamethasone administration could have a confounding effect on the presence of allergic reactions after ICG injection. As such, corticosteroid or antihistamine premedication in patients with iodinated contrast allergies should be considered when standardized ERAS protocols are not utilized, as there are limited data on the rate of allergic or adverse reactions in this population in the absence of these premedications.

One limitation of our study is the small number of patients identified who had a reported iodinated contrast allergy. Iodinated contrast allergies are rare, and documented rates of acute adverse reactions range from 0.2 to 0.7 % with serious reactions being even less common (College, 2023). As such, patients with documented contrast allergies were well represented (25/820 patients, 3.0 %) in this cohort. This study is also limited by the retrospective design, which precludes causal conclusions from being drawn. Allergy assessment for the purposes of this research could not be performed in real time and is limited to what is documented in the medical record. Additionally, the data are collected from a single center utilizing an institution-specific ERAS protocol, limiting the generalizability of this study.

In summary, no patients in this cohort demonstrated an adverse reaction after ICG injection for SLN mapping in endometrial cancer surgical staging. This study supports the reasonable safety of ICG in patients with contrast allergies, particularly when routine ERAS protocols containing dexamethasone are utilized.

5. Author note

This work was presented as a featured oral poster presentation at the Society of Gynecology Oncology Annual Meeting on Women's Cancer in Tampa, FL, on March 25-28, 2023..

CRediT authorship contribution statement

Zainab Balogun: Writing – review & editing, Writing – original draft, Data curation. **Alysia Wiener:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Jessica Berger:** Writing – review & editing. **Jamie Lesnock:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Alison A. Garrett:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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